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Patterns of Recurrence and Survival after Surgery or Stereotactic Radiotherapy for Early Stage NSCLC

Liseth L. van den Berg, MD, Theo J. Klinkenberg, MD,† Harry J. M. Groen, MD, PhD,* and Joachim Widder, MD, PhD‡*

Introduction: Surgery is the standard treatment for early stage non–small-cell lung cancer (NSCLC). For medically inoperable patients, stereotactic ablative radiotherapy (SABR) has emerged as widely used standard treatment. The aim of this study was to analyze survival and patterns of tumor recurrence in patients with clinical stage I NSCLC treated with surgery or SABR.

Methods: Clinical data from all subsequent fluoro-deoxyglucose positron emission tomography/computed tomography-based stage I NSCLC patients (cT1-T2aN0M0) treated with surgery or SABR at our center between 2007 and 2010 were collected. Primary endpoints were overall survival and tumor recurrences/new primary lung tumors. Treatment groups were compared using multivariable Cox regression and competing risk analyses.

Results: Three hundred-forty patients treated with surgery (n = 143) or SABR (n = 197) were included. Surgical patients were younger, had a better WHO performance status and less comorbidities. After adjustment for prognostic covariables, treatment did not influence overall survival (adjusted hazard ratio [HR], SABR versus surgery 1.07; 95% confidence interval [CI]: 0.74–1.54; p = 0.73). Local control and distant recurrence were equal, whereas locoregional recurrences were significantly more frequent after SABR compared with surgery (adjusted sub-HR 2.51; 95% CI: 1.10–5.70; p = 0.028). Nodal failure (HR: 2.16; 95% CI: 1.34–3.48) and distant metastases (HR: 2.12; 95% CI: 1.52–2.97), but not local failure (HR: 1.00; 95% CI: 0.53–1.89) predicted overall survival.

Conclusions: In patients with fluoro-deoxyglucose positron emission tomography/computed tomography-based stage I NSCLC, SABR confers worse locoregional tumor control because of more nodal failures compared with surgery, stressing the need to improve mediastinal and hilar staging.

Key Words: Non–small-cell lung cancer, Early stage NSCLC, Lobectomy, Stereotactic radiotherapy.

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*Department of Pulmonary Diseases, †Department of Cardiothoracic Surgery, and ‡Department of Radiation Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

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Address for correspondence: Harry. J. M. Groen, MD, PhD, Department of Pulmonary Diseases, University of Groningen, University Medical Center Groningen, Hanzeplein 1, PO Box 30.001, 9700 RB Groningen, The Netherlands. E-mail: h.j.m.groen@umcg.nl

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Lobectomy with systematic lymph node dissection is the standard procedure for medically operable patients with stage I non–small-cell lung cancer (NSCLC), with a 5-year survival of 50% to 70%.[1,2] A considerable part of patients with resectable early stage NSCLC is however medically inoperable because of frailty or severe comorbidity.[3] In a cohort of 10,984 patients with early stage NSCLC, surgery was not performed in 23.3% of the white patients and 36% of the black patients. This included inoperable patients as well as patients refusing surgery.[4] The most common reasons for medical inoperability are poor lung function, which is often seen in COPD patients, or cardiovascular comorbidity, both of which bring about an increased risk of postoperative pulmonary complications. When withholding inoperable patients any antitumor treatment, the prognosis is poor and most of them will die because of tumor progression. The 5-year overall survival in untreated patients is 6% or less.[3,5]

From the late 1990s, technological improvements of radiotherapy planning software, verification devices, together with advanced planning-CT techniques (4D-CT) made stereotactic treatment of small tumor volumes with very high doses per fraction possible. With stereotactic ablative radiotherapy (SABR), higher dose in just a few fractions can be delivered and surrounding tissue is much better spared than with 3D-conformal radiotherapy.[6,7] In patients with stage I NSCLC, overall survival and local control rates after SABR are better compared with rates found after conventional 3D-conformal radiotherapy.[8]

Potential clinical advantages of SABR over surgery are the absence of an invasive procedure with possible associated complications, anesthesia, and hospital admission. However, no randomized trials comparing clinical outcomes after either procedure are available.

Several studies have been performed regarding the effect of SABR on survival and tumor control. Soldà et al.[9] reviewed 45 reports analyzing SABR in patients with stage I NSCLC and found survival rates similar to those in a large matched surgical cohort.

A recent large single-center retrospective study, in contrast, found lower 3-year overall survival rates for SABR compared with surgical patients.[10] Local tumor control after SABR is generally good, with previously reported rates ranging between 85% and 98%.[9–14] Few studies were performed comparing the outcomes of a SABR cohort directly with a primarily operable surgical cohort.[10,14–17]

We performed a retrospective study in a large consecutive cohort of patients with clinical stage I NSCLC treated at a single university medical center with surgery or SABR, with the aim to compare survival rates and patterns of tumor recurrence. Comorbidity, age, and performance status were the factors upon which treatment allocation had been based at the multidisciplinary pulmonary oncology panel. Thus, all analyses were adjusted for these factors.

Because of patient selection, we hypothesized a significantly worse unadjusted survival for the SABR cohort that should be equalized after adjustment. Also, we expected comparable adjusted local, locoregional, and distant tumor recurrence rates in the SABR and surgical cohorts using competing risk analysis.

PATIENTS AND METHODS

Patients

The study was conducted at the University Medical Center Groningen in the Netherlands. Because all data in this study were obtained from patient medical records and patients themselves were not involved in the study, neither approval of the Institutional Review Board nor informed consent were required according to Dutch law.

All consecutive patients treated between January 2007 and July 2010 with curatively intended surgery or SABR for proven or suspected fluoro-deoxyglucose positron emission tomography–computed tomography (FDG-PET–CT)-staged NSCLC were selected from the database.

Inclusion and Exclusion Criteria

Patients with cT1-2aN0M0 tumors (less than 50 mm) according to the 7th TNM edition were included[18] (Fig. 1). Staging was based on FDG-PET/CT. Furthermore, inclusion required cytological or histological confirmation of the tumor or, in absence of a pathological confirmation, a combination of imaging information requiring increased FDG-PET-uptake and/or a growing or new lesion on CT exhibiting signs of malignancy. FDG-avid or CT-enlarged (greater than 10 mm short axis diameter) lymph nodes were examined with mediastinoscopy or endosonography with fine-needle aspiration to confirm that their nodes are free of tumor. Patients with a preoperatively proven benign lesion, lung metastases, small-cell lung cancer, or lymph node metastases were not included as well as patients with neoadjuvant chemotherapy or radiotherapy (Fig. 1). Patient allocation to treatment required discussion at the multidisciplinary pulmonary oncology panel.

Treatment Procedures

Surgery was performed via open thoracotomy (94% of the cases) or video-assisted thoracic surgery and included wedge resection, lobectomy, bilobectomy, or pneumonectomy, the latter three operations with hilar and mediastinal lymph-node dissection. SABR was based on a 4D-planning CT. The planning target volume (PTV) was defined as the envelope including the moving gross tumor volume plus a margin in all directions of 5 mm. After the institutional protocol, a risk-adapted fractionation schedule of 3 to 12 fractions to 60 Gy was administered using a Novalis accelerator, online position verification and correction was performed using the Exac-Trac system with a 6D-robotic couch (Brainlab, Feldkirchen, Germany).[8] In brief, lesions completely surrounded by lung tissue and not located within 2 cm of the central airways received three fractions of 20 Gy. Lesions located within the 2 cm corridor of trachea and main bronchi received eight fractions of 7.5 Gy or 12 fractions of 5 Gy, whereas lesions adjacent to the thoracic wall received five times 12 Gy. During the study period, a pencil-beam dose-calculation algorithm with tissue heterogeneity correction had been used and the dose was prescribed at 80% isodose comprising periphery of the PTV.[8]

Follow-Up

Patient data were extracted from the hospital patient files and supplementary information was retrieved via

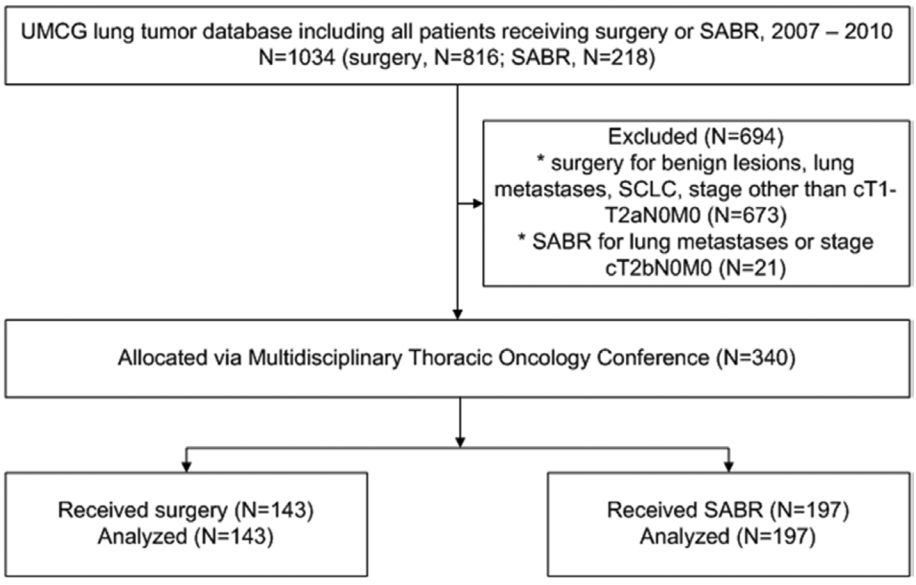

FIGURE 1. Consort diagram.

telephone contact with general practitioners. Patients' vital status was additionally obtained from the Municipal Personal Records Database with a cutoff on January 30, 2014. During follow-up, regular CT scans were made to monitor tumor recurrences 3 and 6 months after treatment, then at 6 months intervals until 2 years and yearly thereafter. FDG-PET was only performed when clinically indicated. Tumor recurrence was scored in case of greater than 20% tumor growth (after SABR), new lesions on CT or brain MRI, or a confirmatory FDG-PET showing high FDG uptake in the lesion.

Study Endpoints

The endpoints of the study were overall survival and local, nodal, locoregional (=local or nodal or both), and distant tumor recurrence or new pulmonary tumors. To score local recurrence in a study comprising patients with lobectomy, pneumonectomy, wedge resection, and SABR is highly challenging. In this study, local recurrence after both surgery and SABR was defined as a growing tumor in the same lobe as the primary tumor including growth at the irradiated location (the PTV) or around the surgical clips including the ipsilateral hilus. Tumor occurring in another lobe or extrathoracic tumor was defined as distant metastasis. Locoregional tumor recurrence was defined as local recurrence as defined above plus any mediastinal or hilar lymph node metastasis.

Statistics

Overall survival was estimated using the Kaplan–Meier method. Time was taken between the date of surgery or the first fraction of SABR and date of death because of any cause or most recent date alive. To determine the role of covariables on overall survival, Cox regression analyses were performed. The following covariables were analyzed: treatment, age, sex, WHO performance score, Charlson comorbidity index, and tumor size. Significant factors were included in the multivariable models. For tumor recurrences and metastases, multivariable competing risk analyses with death and nontarget-type (first) recurrences as competing risk were performed. With this method, it is possible to correct for differences in intercurrent death and censoring because of clinical necessities. For example, occurrence of distant metastases was a competing risk for local recurrence, because imaging to identify local recurrence had been ceased in these patients. Thus, they were no longer at risk for local recurrence, a fact that is neglected in e.g., Cox regression analysis.

RESULTS

Patient, Tumor, and Treatment Characteristics

A total of 340 patients treated with surgery (n = 143) or SABR (n = 197) were included. Patient and treatment characteristics are shown in Table 1. Patients treated with surgery were 10 years younger, had a better performance status, less comorbidity, and better lung function tests, but tumor size and clinical stage were not different. FDG-PET/CT was used for staging in all patients, endoscopic ultrasound and cervical mediastinoscopy were only used in 1% and 4%, respectively. Of note, in 85 of the surgical patients (59%), no tumor tissue had been obtained before surgery, although in 59 of them (69%) one or more biopsies had been attempted. In 154 of the SABR patients (78%), no tumor tissue was obtained.

Significantly more patients in the surgical cohort had an FDG-negative primary tumor ($p < 0.001$). The indication for resection in these cases had been based on spiculation and tumor growth on repeated CTs.

For surgical patients, the median hospital stay was 9 days with a range of 3–111 days; in 90% of the patients, admission was less than 25 days. Stereotactic radiotherapy was exclusively administered in an outpatient setting.

In the surgical cohort, 15% of the patients received adjuvant chemotherapy and 2% had postoperative radiotherapy for incomplete resection. Only a single patient (less than 1%) had adjuvant chemotherapy after SABR ($p < 0.001$).

Overall Survival

Median follow-up was 61 months. Age, performance status, comorbidity, tumor size, and treatment (surgery better than SABR) were highly significant predictive factors for survival at univariable analysis. After adjustment for the former factors, the difference in survival between surgery and SABR disappeared and the adjusted SABR versus surgery hazard ratio (HR) for overall survival was 1.07 (95% confidence interval [CI]: 0.74–1.54; $p = 0.73$). Of note, adjuvant therapy was not significantly related to overall survival. Unadjusted survival rates are shown in Table 2.

Tumor Recurrences and Occurrence of New Primaries

Local tumor control using the definition as described above was not different between SABR and surgery (adjusted sub-HR 1.21; 95% CI: 0.38–3.90; $p = 0.75$). Also for distant recurrence, no significant difference was found between both treatments (adjusted sub-HR 1.01; 95% CI: 0.56–1.84; $p = 0.97$). Treatment was not a significant factor for nodal tumor recurrence, but a trend for more nodal recurrences after SABR was found (adjusted sub-HR 2.17; 95% CI: 0.91–5.17; $p = 0.079$).

Locoregional recurrences however—local or nodal or both together—were significantly more frequent after SABR compared with surgery (adjusted sub-HR 2.51; 95% CI: 1.10–5.70; $p = 0.03$; Fig. 2).

Nodal and distant metastases, but not local recurrence, were significant independent predictive factors for survival (Table 3). The gross pattern of recurrence is displayed in Table 4. Unadjusted freedom-from-tumor-recurrence rates are shown in Table 2.

DISCUSSION

For medically inoperable patients with early stage NSCLC, SABR has evolved as the preferred treatment option.[19,20] There are no randomized comparative trials available comparing surgery with SABR. However, such trials would by definition be confined to operable patients. Therefore, the evolution of SABR has been mainly triggered by promising results for local tumor control after SABR.[9–14,21]

TABLE 1. Demographic, Clinical, and Treatment Characteristics of Included Patients (n = 340)

	Surgery (n = 143)	SABR (n = 197)	p Value
	No. of Patients (%)	No. of Patients (%)	
Age, years			<0.001
Median	67	77	
Range	40–84	52–93	
Sex			NS
Men	96 (67)	143 (73)	
Women	47 (33)	54 (27)	
WHO performance score			<0.001
0–1	143 (100)	155 (79)	
2–3	0 (0)	42 (21)	
Charlson comorbidity index			0.012
Median	2	2	
Range	0–5	0–5	
0–1	65 (45)	77 (39)	
≥2	78 (55)	120 (61)	
Current or former smoker	124 (87)	195 (99)	<0.001
cTNM classification			NS
cT1aN0M0	61 (43)	71 (36)	
cT1bN0M0	22 (15)	55 (28)	
cT2aN0M0	60 (42)	71 (36)	
Tumor size in mm, median (range)	23 (5–50)	25 (5–50)	NS
Tumor location			NS
Right upper lobe	51 (36)	73 (37)	
Right middle lobe	9 (6)	9 (5)	
Right lower lobe	25 (18)	26 (13)	
Left upper lobe	36 (25)	55 (28)	
Left lower lobe	22 (15)	34 (17)	
Surgical treatment			
Pneumonectomy	5 (3)		
Lobectomy	110 (77)		
Bilobectomy	11(8)		
Wedge resection	17 (12)		
pTNM classification			
pT1aN0M0	50 (35)		
pT1bN0M0	23 (16)		
pT2aN0M0	30 (21)		
upstaged to >stage I:	35 (24)		
pT1a-2aN1M0	16 (11)		
pT1a-2aN2M0	11 (8)		
pT2bN0-2M0	8 (6)		
Other tumor[a]	2 (1)		
Benign[b]	3 (2)		
SABR schedule			
3 × 20 Gy		95 (48)	
5 × 12 Gy		59 (30)	
8 × 7.5 Gy		39 (20)	
12 × 5 Gy		4 (2)	
Follow-up time, months			NS
Median	61	61	
Range	43–84	43–79	

[a]One melanoma; one salivary gland tumor.
[b]One solitary fibrous tumor; two localized infections.
WHO, World Health Organization; SABR, stereotactic ablative radiotherapy; NS, not significant.

The range of reported survival rates after SABR is understandably variable because of patient selection.[9] Moreover, little is known about the reasons for decreased survival after SABR: is it mainly because of comorbidity prompting medical inoperability, or is it because of differences in patterns of recurrence, or to both factors. To date, few studies have accepted the challenge to compare the outcomes of a SABR cohort directly with a surgical cohort.[15–17,22]

Typically, younger and fitter patients with less comorbidity and better lung function are offered surgery for solitary FDG-positive lung lesions highly suspicious for NSCLC, whereas the medically marginally operable or inoperable patient is offered SABR. In the absence of randomized data, comparative survival and recurrence data corrected for these well-known selection parameters are the second best source to possibly inform clinical decision making. To analyze survival rates, patterns of tumor recurrence after surgery or SABR, and the impact of recurrence patterns upon survival, we studied a consecutive cohort of patients with cT1-2aN0M0 lung tumors highly suspicious for NSCLC. Our hypothesis was that SABR, when adjusting for group differences, would be equally effective as surgery in terms of tumor control and survival.

Our study indeed showed that survival depended on age, performance status, comorbidity, and tumor size, and that adjusted overall survival after surgery or SABR was not different. Prospective single arm trials involving SABR and retrospective analyses comparing SABR with surgery have found similar overall survival rates as we have found in our study.[10–12,23] A recently published review showed even similar 2- and 3-year overall survival rates after SABR and surgery.[9]

TABLE 2. Unadjusted Survival and Freedom-from-Recurrence Rates (%)

	1 Year	2 Years	3 Years	5 Years
Overall survival				
Surgery	91.6	80.4	68.5	58.2
SABR	88.3	76.6	56.9	31.8
Free from local recurrence				
Surgery	98.3	97.2	96.0	93.0
SABR	98.9	95.9	95.1	80.0
Free from lymph node recurrence				
Surgery	97.4	92.4	90.1	87.3
SABR	92.0	88.3	88.3	78.7
Free from locoregional recurrence				
Surgery	97.4	92.4	90.1	87.3
SABR	90.9	85.6	84.8	77.2
Free from distant recurrence				
Surgery	89.9	82.7	76.8	74.1
SABR	91.5	85.0	80.6	65.9
Free from any recurrence				
Surgery	89.1	82.7	76.8	71.7
SABR	84.7	77.8	72.7	57.4

Locoregional recurrence = local or lymph node or both.
SABR, stereotactic ablative radiotherapy.

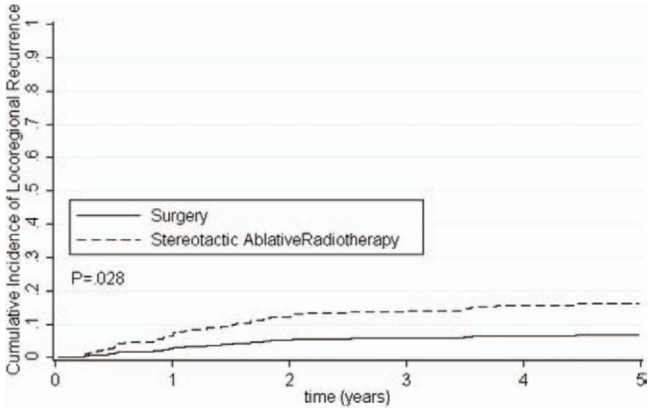

FIGURE 2. Cumulative incidence of locoregional failure after surgery or stereotactic radiotherapy based on competing risk analysis.

Also, the largest retrospective single-center SABR analysis showed comparable survival and recurrence rates.[21]

Lagerwaard et al.[13], who analyzed potentially operable patients having received SABR, found higher overall survival rates compared with our study because of selection of a fitter patient group. An even higher 5-year overall survival of 69.5% was found by Onishi et al.[24], however, this was a cohort of 87 medically operable Japanese patients treated with SABR, who show better survival very consistently in most studies involving lung cancer.

In our study, we defined local tumor recurrence as recurrence in the same lobe as the primary tumor or at the ipsilateral hilus, and locoregional recurrence as including in addition the contralateral hilus or any mediastinal lymph node metastases. Tumor recurrence definitions are not used consistently in the literature. In most stereotactic radiotherapy or local-and-limited-resection studies, local recurrence is defined more restrictive as recurrence at the exact location of the primary tumor.[23] Such a definition precludes reasonable comparisons with lobectomy series. In our study, no difference between the treatment groups was found for local recurrence (using our definition) or distant metastases. In contrast to other studies that found no increased locoregional recurrence rate after SABR compared with resection,[16,22] we observed a trend toward more nodal recurrences after SABR and significantly more locoregional tumor recurrences after SABR compared with surgery. In keeping with this result, 24% (19% were solely because of hilar and/or mediastinal lymph nodes) of our FDG-PET-CT-based clinical stage I patients were upstaged postoperatively to higher stages based on the resected specimen (Table 1). This seems to be quite high and may partly be because of an earlier generation PET machine that was used during the time of the study, but it is in line with recent data in the literature.[16,25,26] This stresses the importance of optimal lymph node staging especially if the nodes are not sampled at treatment (i.e., SABR or wedge resection). Even though our patients had undergone FDG-PET, still a number of them will have harvested latent metastases in hilar or mediastinal nodes, which were not treated with SABR. A major argument for surgery thus remains the remaining uncertainty about hilar (or mediastinal) lymph node involvement despite negative CT and FDG-PET scans. It is well known that small lymph node metastases are not detected by PET. A recently published study showed that the sensitivity, specificity, and accuracy of 18F-FDG-PET/CT for assessing mediastinal lymph node metastasis with a short-axis diameter of less than 15 mm is still limited.[27] As high as 18% of occult lymph node metastases in an FDG-negative hilus and mediastinum were found in another recent study, and SUV and size of primary tumor were factors predicting node-positivity.[28] Therefore, to improve locoregional tumor control in patients with stage I NSCLC who are eligible for SABR, using new-generation PET and even minimally invasive mediastinal staging using E(B)US with fine needle aspiration or even mediastinoscopy should be carefully considered to spare them potential undertreatment because of neglect of nodal metastases.

A limitation of our study is its retrospective design. However, we double-checked data using information from the general practitioner and the Municipal Personal Records Database in addition to patient files. A serious limitation of the Charlson comorbidity score is that no distinction is made in severity of the comorbidity, e.g., between mild or severe pulmonary problems. Another limitation is because of use of an out-dated radiation dose calculation algorithm during the study period (pencil-beam calculation with heterogeneity correction). Nowadays, Monte Carlo or collapsed cone algorithms are used resulting in higher SABR doses compared with the doses actually delivered during the studied period. Therefore, locoregional tumor control with SABR might have improved in the last couple of years. The strength of this study is the direct comparison of both survival and patterns of tumor recurrence between a large surgical and a large SABR consecutive cohort

TABLE 3. Multivariable Cox-Model of Factors Predicting Overall Survival

Variable	Hazard Ratio	95% CI	*p* Value
Age, per year	1.041	1.02–1.06	<0.001
Charlson comorbidity index, ≥2 vs. 0–1	1.453	1.07–1.98	0.017
WHO performance score, ≥2 vs. 0–1	2.025	1.35–3.04	0.001
Tumor size, per mm	1.013	1.00–1.03	0.061
Treatment, SABR vs. surgery	0.98	0.68–1.41	0.915
Local recurrence	0.996	0.53–1.89	0.991
Lymph node recurrence	2.163	1.34–3.48	0.002
Distant recurrence	2.123	1.52–2.97	<0.001

WHO, World Health Organization; SABR, stereotactic ablative radiotherapy; CI, confidence interval.

TABLE 4. Patterns of Failure per Treatment Group (n = 340)

	Surgery	SABR
	(n = 143)	(n = 197)
Type of Recurrence	**No. of Patients (%)**	**No. of Patients (%)**
Local	6 (4)	11 (6)
Lymph node	12 (8)	25 (13)
Local or node or both	12 (8)	30 (15)
Distant	29 (20)	41 (21)
Any	31 (22)	57 (29)
No recurrence	112 (78)	140 (71)

Local, recurrence in lobe of primary tumor or ipsilateral hilus; lymph node, recurrence in any hilar or mediastinal lymph node; local or node or both = locoregional; distant, recurrence outside locoregional region; any, any of the above recurrence types.
SABR, stereotactic ablative radiotherapy.

with a very long follow-up. Indications were discussed at a multidisciplinary tumor board, all patients were staged with FDG-PET/CT, and analyses were based on clinical, not postoperative pathological staging information, which would skew the comparison. Analyses were corrected for the factors upon which patient selection for treatment had been performed and patterns of recurrences were analyzed taking competing risks into account. In conclusion, patients with NSCLC at clinical stage I treated with surgery were 10 years younger, fitter and had less comorbidities than those treated with SABR. Adjusted overall survival was similar between surgery and SABR, but SABR yielded worse locoregional tumor control compared with surgery. This was because of more nodal failures after SABR compared with surgery. SABR is a tailor-made treatment for patients unfit for surgery, but optimal mediastinal and hilar staging remains essential for optimizing treatment decisions.

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